IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kim

Serial No.: 10/723,401 Examiner: Snow, Bruce, Edward

Filed: November 26, 2003 Art Unit: 3738

For: POROUS BIOCERAMICS FOR BONE SCAFFOLD AND METHOD FOR MANUFACTURING THE SAME

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

We, Hyoun-Ee Kim and Hae-Won Kim, declare the following:

1. We are the joint inventors of the subject matter described and claimed in the United States Patent Application Serial No. 10/723,401, filed November 26, 2003, entitled Porous Bioceramics For Bone Scaffold And Method For Manufacturing The Same, which subject matter is disclosed and claimed in the above-referenced patent application.

2. We are two of the co-authors of an article entitled "Porous ZrO_2 bone scaffold coated with hydroxyapatite with fluorapatite intermediate layer" published on August 19, 2003, and are the joint inventors of the subject matter which is disclosed in this publication and disclosed and claimed in the above-referenced patent application.

3. A copy of the article entitled "Porous ZrO_2 bone scaffold coated with hydroxyapatite with fluorapatite intermediate layer" published on August 19, 2003, is attached as Exhibit A.

4. In addition to ourselves, there are five other co-authors of the listed article: Seung-Yong Lee, Chang-Jun Bae, Yoon-Jung Noh, Hyun-Man Kim, and Jea Seung Ko. While these individuals are co-authors of the publication, they are not co-inventors of the subject matter described therein.

5. The five other co-authors, Seung-Yong Lee, Chang-Jun Bae, Yoon-Jung Noh, Hyun-Man Kim, and Jae Seung Ko, as reported by Dr. Hyun Kim and Young-Dong Kim of the Seehang Law Offices, were just assistants and not inventors of the subject matter disclosed in the publication. Since the entities are not different, the publication is not prior art under 35 U.S.C. 102 (a) or (e).

6. A copy of the letter from Hyun Kim and Young-Dong Kim of the Seehang Law Offices to Mr. Schmeiser dated September 5, 2006, is attached as Exhibit B.

7. We, Hyoun-Ee Kim and Hae-Won Kim, are in fact the joint inventors of the subject matter disclosed in the publication. The subject matter disclosed in the publication originated with us. Thus, this publication cannot be used against Applicants since it does not satisfy the 1 year time requirements of 35 U.S.C. 102 (b).

8. This declaration clearly complies with the requirements set forth in MPEP 716.10 Attribution, as detailed by the Examiner in the Office Action mailed Jan 23, 2007.

9. We further declare that all statements made herein of our own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: 6/22/2007 By: Hyoun-Ee Kim
Hyoun-Ee Kim

Date: 6/22/2007 By: Hae-Won Kim
Hae-Won Kim

EXHIBIT A

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Porous ZrO_2 bone scaffold coated with hydroxyapatite with fluorapatite intermediate layer

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Abstract

Highly porous zirconia (ZrO_2) bone scaffolds, fabricated by a replication technique using polymeric sponge, were coated with hydroxyapatite (HA). To prevent the chemical reactions between ZrO_2 and HA, an intermediate fluorapatite (FA) layer was introduced. The strength of the porous ZrO_2 was higher than that of pure HA by a factor of 7, suggesting the feasibility of ZrO_2 porous scaffolds as load-bearing part applications. The coated HA/FA layer, with a thickness of about 30 μm, was firmly adhered to the ZrO_2 body with a bonding strength of 22 MPa. The osteoblast-like cells were attached and spread well on the coating layer throughout the porous scaffolds. The alkaline phosphatase activity of the proliferated cells on the HA/FA coated ZrO_2 was comparable to that on pure HA and higher than that on pure ZrO_2.

Keywords: ZrO_2 porous scaffold; HA coating; FA intermediate layer; Compressive strength; Adhesion strength; Cellular response

1. Introduction

Human bones are composed of highly interconnected inorganic hard tissues (calcium phosphates) and organic soft components (collagen fibers). In cortical bone, cylindrical channels of osteons are held together by the framework, whilst in cancellous bone, the framework is highly open-spaced [1]. Many attempts have been made to mimic the interconnected framework structure of bone in terms of structural and biological characteristics. In those studies, it was found that a minimum pore size of ~100 μm was necessary for bone ingrowth into the channels [2]. As a porous bone graft material, hydroxyapatite [HA; $Ca_{10}(PO_4)_6(OH)_2$] ceramics have attracted a great deal of attention due to their excellent biocompatibility and bioaffinity [3–7]. However, there are critical limitations in applying the HA to real systems because of its poor mechanical properties, such as strength and fracture toughness [8]. Consequently, the use of porous HA has been restricted to the powders, granules, and non-load bearing small parts.

On the other hand, zirconia (ZrO_2) and its composites possess excellent mechanical properties. Several researchers have successfully fabricated porous ZrO_2 bodies for biomedical applications [9,10]. However, ZrO_2 did not bond directly to bone nor conduct bone ingrowth into the pore channel [11]. Consequently, biocompatible materials need to be coated onto the surface or be incorporated as second phases [12,13]. In this context, a porous ZrO_2 body was chosen as a framework for load-bearing and the HA was used as an outer coating layer to enhance the biocompatibility and osteoconductivity. The HA coatings on bioinert materials were reported to have advantages in surgical applications due to the rapid fixation and bonding to bones as well as uniform ingrowth at the interface [14,15]. However, there is a serious problem in incorporating the ZrO_2 body with HA coating; reactions between the ZrO_2 and the HA. Those reactions not only reduce the mechanical properties but also degrade the biocompatibility of the material [16,17]. Therefore, to fabricate a ZrO_2 body coated with HA, it is necessary to suppress the reaction between HA and ZrO_2.

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Previously, it was observed that different from HA fluorapatite [FA, $Ca_{10}(PO_4)_6F_2$] is chemically inert with respect to ZrO_2 even at elevated temperatures [16,17]. Therefore, it is possible to form a stable HA coating layer on the ZrO_2 scaffold if FA is introduced as an intermediate layer between the ZrO_2 and the HA. In this study, we fabricated porous ZrO_2 bodies by a sponge replication technique and coated the body with FA and subsequently with HA by the powder slurry method. The coated biomaterial was characterized in terms of composition, mechanical properties, morphological evolution, and the in vitro cellular responses.

2. Materials and methods

2.1. Fabrication of porous scaffold

As a starting material for the porous body, commercial ZrO_2 powder (3 mol% Y_2O_3, Cerac Inc., WI, USA) was used to prepare a slurry mixture. The powder of 100 g was stirred vigorously in 150 ml distilled water dispersed with a triethyl phosphate (TEP; $(C_2H_5)_3PO_4$, Aldrich, USA) of 6 g for 24 h. As a binder, poly vinylbutyl (PVB, Aldrich, USA) of 6 g was dissolved in another beaker, which was subsequently added to the slurry and stirred for an additional 24 h.

A polyurethane foam template (45 ppi, Customs Foam Systems Ltd, Canada) was cut to the appropriate dimensions for fabricating porous scaffolds. The prepared sponge was immersed in the slurry and subsequently blown with an air gun to disperse the slurry uniformly throughout the porous scaffolds without blocking the pores. The sponge was then dried at 80 °C for 10 min. These dipping-and-drying steps were repeated 4 times. The sponge was then oven dried at 80 °C for 12 h. The obtained body was heat treated to burn out the sponge and binder at 800 °C for 5 h at a heating rate of 2 °C/min, and at 1400 °C to solidify and finally to obtain a dense ZrO_2 porous scaffold.

By repeating the above replication process (2–5 times), it was possible to reduce the porosity of the structure. For the purpose of comparison, a HA porous body was fabricated also from the HA slurry mixture using the same procedure as for ZrO_2 with the only difference being the heating cycle; the final heat treatment was done at 1250 °C for 3 h instead.

2.2. HA/FA coating on porous body

Commercially available HA (Alfa Aesar Co., USA) and in-house fabricated FA powder were used as starting slurries for the coating process [17]. Each powders of 15 g were mixed with TEP and PVB in 50 ml ethanol, and stirred for 24 h to prepare the HA and the FA slurry. The fabricated ZrO_2 porous body was immersed in the FA slurry and dried at 80 °C for 3 h. This was followed by heat treatment at 800 °C for 5 h for binder burnout and at 1200 °C for an additional 1 h to prepare the FA coating. The process was repeated twice to obtain a uniform FA layer. The FA-coated body was immersed in the HA slurry, dried and heat-treated following the same procedures. By this repeated process, a HA/FA double-layer coated ZrO_2 porous body was obtained. For a comparison, HA was coated directly onto the ZrO_2 body without the FA layer.

2.3. Characterization and test

The porosity of the bodies was calculated by measuring their dimensions and weights. For a compressive strength test, porous specimens with dimensions of $5 \times 5 \times 10$ mm were axially loaded at a crosshead speed of 0.05 mm/min. Both edges were impregnated with paraffin to eliminate the edge fracture. The phase and the morphology of the coated bodies were analyzed using X-ray diffraction (XRD) and scanning electron microscopy (SEM), respectively. The adhesion strength of the coating layer was tested with an adhesion testing apparatus (Sebastian V, Quad Group, Spokane, WA, USA). A stud pre-coated by the manufacturer using an epoxy of a proprietary composition was adhered to the coating layer by curing the epoxy at 150 °C for 1 h. The stud with diameter of 1.69 mm was pulled with a loading rate of ~2 mm/min until the coating layer failed, and the bond strength was calculated from the maximum load recorded.

2.4. In vitro cellular assay

The human osteosarcoma (HOS) cell line was used after being cultured in flasks containing Dulbecco's modified Eagle's medium (DMEM, Life Technologies Inc., MD, USA) supplemented with 10% fetal bovine serum (FBS, Life Technologies Inc., MD, USA). The cells were then plated at a density of 1×10^4 cells/ml on a 24-well plate containing the fabricated porous specimens (HA/FA coated ZrO_2, HA, and ZrO_2) and cultured for 5 and 21 d in an incubator humidified with 5% CO_2/95% air at 37 °C. After culturing for 5 days, the morphology of the proliferated cells was observed with SEM after fixation with glutaraldehyde (2.5%), dehydration with graded ethanol (70%, 90%, and 100%), and critical point drying.

For an assessment of the alkaline phosphatase (ALP) activity, the cells were cultured for 21 d. After decanting the culture media, the cell layers were washed once with Hank's balanced salt solution (HBSS), followed by a detachment with Trypsin-EDTA solution for 10 min. After centrifugation at 1200 rpm for 7 min, the cell pellets were washed once with PBS and resuspended by vortexing in 200 μl of 0.1% Triton X-100. The pellets

were disrupted further by 7 freezing/thawing cycles. After centrifugation at 13,000 rpm in a microcentrifuge for 15 min at 4 °C, the cell lysates were assayed colorimetrically for their ALP activity using *p*-nitrophenyl phosphate as a substrate at a pH 10.3 (Sigma Kit, as described fully in procedure no. 104). Each reaction was initiated with *p*-nitrophenyl phosphate, and allowed to react for 60 min at 37 °C, which was then quenched on ice. The *p*-nitrophenol produced was measured at 410 nm using spectrophotometer.

3. Results

3.1. ZrO_2 porous scaffolds

Typical structures of the as-fabricated ZrO_2 porous scaffolds with various porosities are shown in Figs. 1 (A)–(C). By repeating the replication process, it was possible to obtain porous bodies with different degrees of porosity (92–74%). After a single replication, a highly uniform porous structure with the porosity of 92% was obtained (Fig. 1(A)). Spherical macropores with a diameter of ~600 μm and the stems with diameters of 100–200 μm formed a perfectly interconnected pore structure. The shape of the pores and stems maintained the initial polyurethane structure without blocking the pores or destroying the framework. By repeating the replication process three times, the stems became thicker and the porosity decreased to 83%. Even though the initial shape of the framework was slightly altered, there was little blocking of pores (Fig. 1(B)). Further replications decreased the porosity steadily until the pores were partly blocked as shown in Fig. 1(C). However, the body still retained a highly interconnected pore structure with a dense ZrO_2 framework.

Fig. 2 shows the porosity change of the ZrO_2 scaffolds as a function of the replication cycle. The porosity decreased steadily with increasing the replication cycle. An approximately 4–5% reduction in porosity was observed with each cycle. After repeating the procedure for 5 times, a porosity of 74% was obtained. Based on these results, the porosity was controlled by changing only the number of replication cycles.

To investigate the mechanical properties of the fabricated ZrO_2 scaffold, the compressive strength was measured and compared with that of pure HA body, as shown in Fig. 3. The strength of ZrO_2 was markedly higher than that of pure HA: with equivalent porosities, the strength of ZrO_2 was about 7 times higher than that of pure HA. The strength of the ZrO_2 ranged from 1.6 to 35 MPa when the porosity was between 92% and 74%, while that of HA was in the range of 0.3–5 MPa with equivalent porosities.

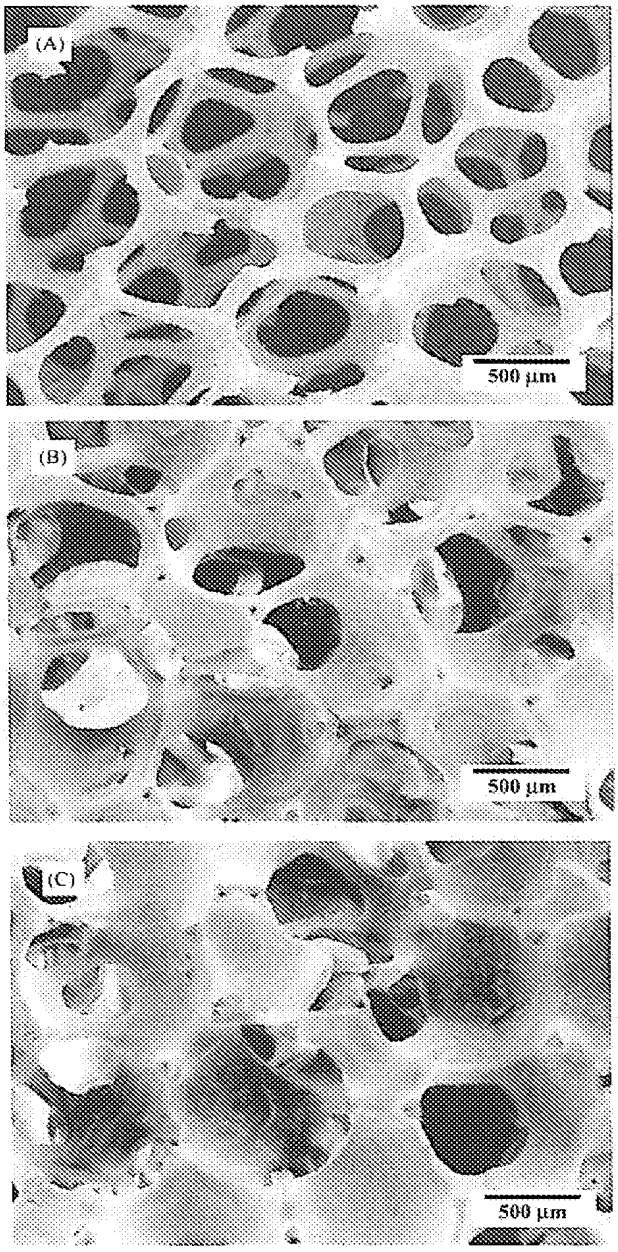

Fig. 1. Macroscopic structures of the ZrO_2 porous bodies with a porosity of (A) 92%, (B) 84%, and (C) 74%.

3.2. Phase and morphology of HA/FA coating layer

The ZrO_2 body with the porosity of 92% was coated with HA layer. To prevent chemical reactions between the HA and ZrO_2, the FA layer was coated on the ZrO_2 surface prior to the HA coating. The effect of the FA intermediate layer on the stability of HA as well as ZrO_2 is well illustrated by the XRD patterns shown in Fig. 4.

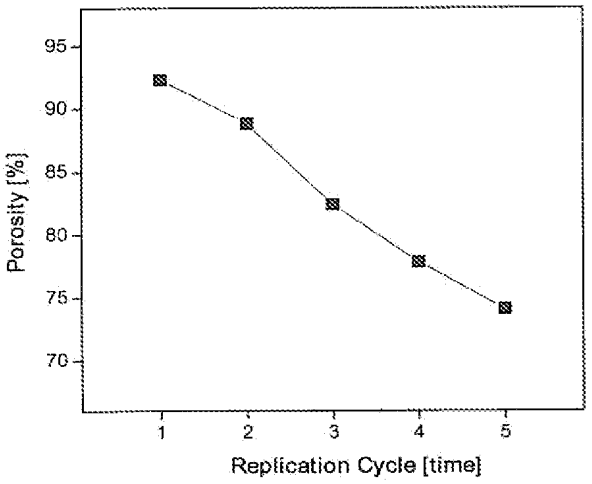

Fig. 2. Porosity of ZrO_2 body with respect to the number of replication cycles.

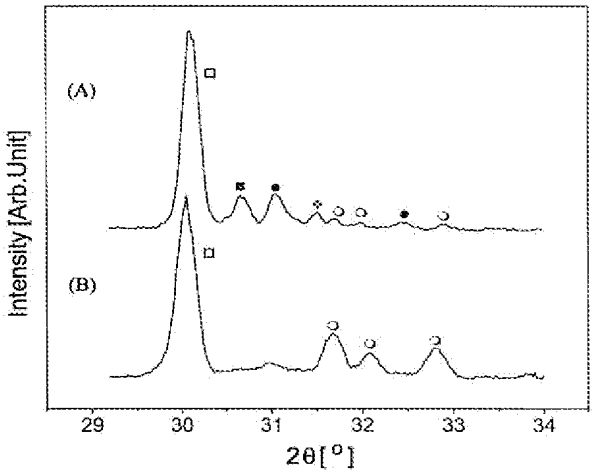

Fig. 4. XRD patterns of ZrO_2 coated with HA; (A) without the intermediate layer and (B) with FA intermediate layer: (○) HA, (□) ZrO_2, (●) β-TCP, (■) α-TCP, and (◆) $CaZrO_3$.

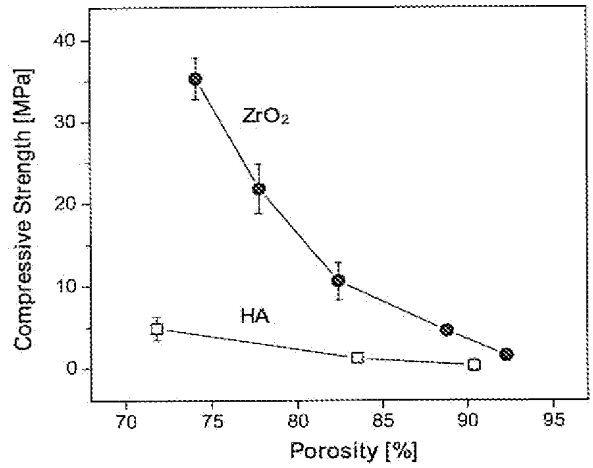

Fig. 3. Compressive strengths of porous ZrO_2 and HA as a function of the porosity.

Without the FA layer, considerable amount of α-and β-TCP as well as $CaZrO_3$ were formed after heat treatment at 1250 °C, as shown in Fig. 4(A). Naturally, the HA peaks were very weak, confirming the reaction between HA and ZrO_2 [16,17]. On the other hand, when the FA was pre-coated, no such reaction products were detected as shown in Fig. 4(B). These results clearly illustrate the effect of the FA layer on suppressing the reactions between HA and ZrO_2.

The SEM morphologies of HA/FA coating layer on ZrO_2 are shown in Figs. 5. The ZrO_2 framework was uniformly coated with HA/FA as shown in Fig. 5(A). A cross section also shows a uniform coating layer with thickness of ~30 μm (Fig. 5(B)). At higher magnification, the HA layer was distinguishable from the FA layer as shown in Fig. 5(C). The thicknesses of the FA and HA layers are ~5 and ~20 μm, respectively. There were no delamination or cracks at both interfaces of HA/FA and FA/ZrO_2, indicating relatively tight bondings among the layers. The bond strength was in the range of 20–30 MPa without much variation depending on the heat treatment temperature. The detached surface was observed with SEM after the strength test. The failure occurred mainly at the FA/ZrO_2 interface as shown in Fig. 6. However, fragments of the coating layer still remained on the surface (arrows), which was confirmed by EDS analyses.

3.3. Cellular responses

For an assessment of the cellular response to the HA/FA coated ZrO_2 scaffolds, the osteoblast-like HOS cells were seeded on the fabricated materials. Figs. 7 show the cell growth morphologies on the HA/FA coated ZrO_2 after culturing for 5 days. The cells spread well and migrated deep into the large pores, suggesting the osteoconducting characteristics of the porous scaffolds (Fig. 7(A)). The cells were uniformly proliferated throughout the porous structure. At higher magnification, it is clearly observed that the cell membranes spread well with an intimate contact with the coated surface, as shown in Fig. 7(B).

The differentiation characteristics of the cells were evaluated by the ALP expression level after culturing for 21 days, as shown in Fig. 8. Pure HA with the same structure and ZrO_2 without coating were also tested for the purpose of comparison. The ALP activities of the HOS cells on all porous materials showed higher ALP

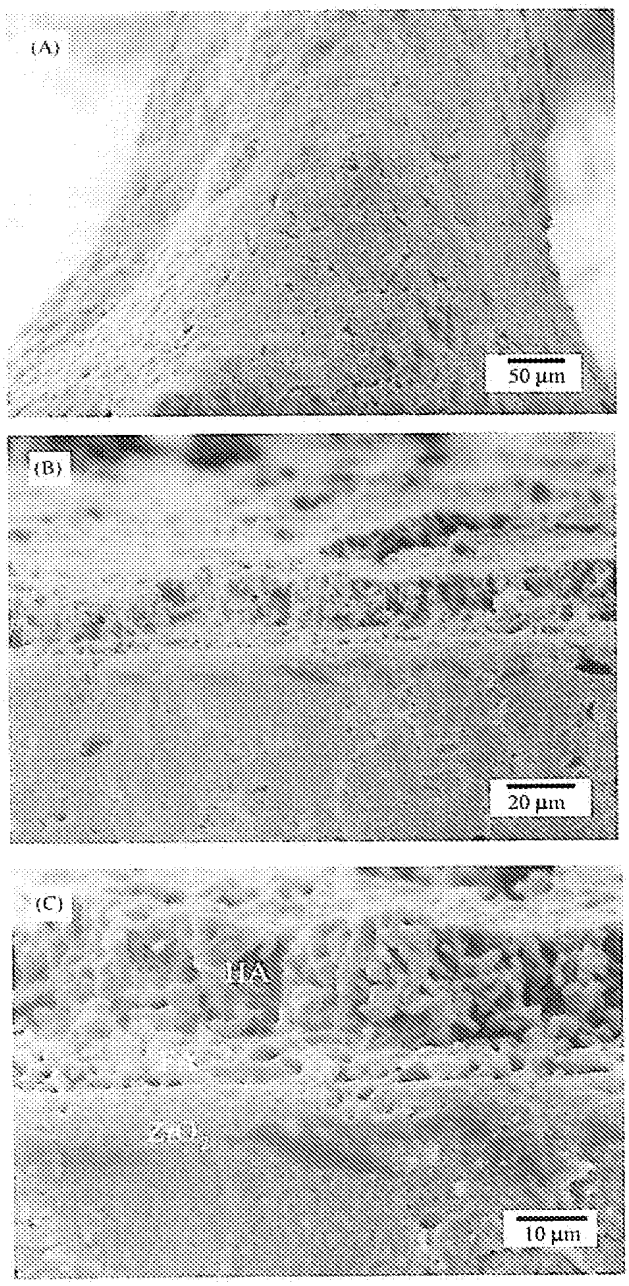

Fig. 5. Morphologies of HA/FA layer on the ZrO_2 substrate; (A) plane view (B) cross sectional view and (C) cross sectional view with high magnification.

expression level compared to the cell culture dish. In particular, the HA/FA coated ZrO_2 sample exhibited a similar ALP expression level with respect to the pure HA body. As expected, the differentiation on the ZrO_2 without coating was lower than that on the coated sample.

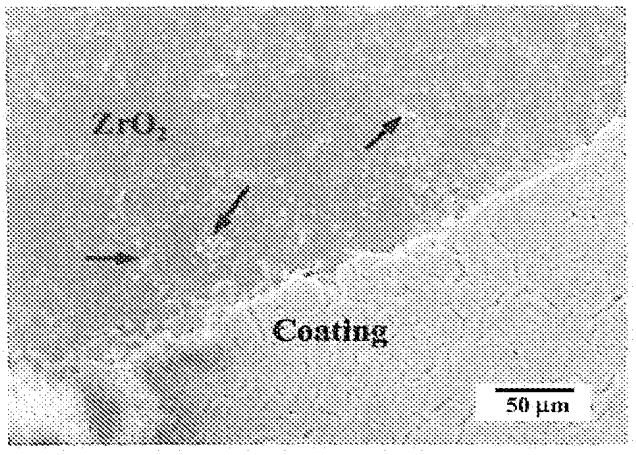

Fig. 6. SEM micrograph on the detached area of the coating layer. Arrows indicate the remanent of the coating layer.

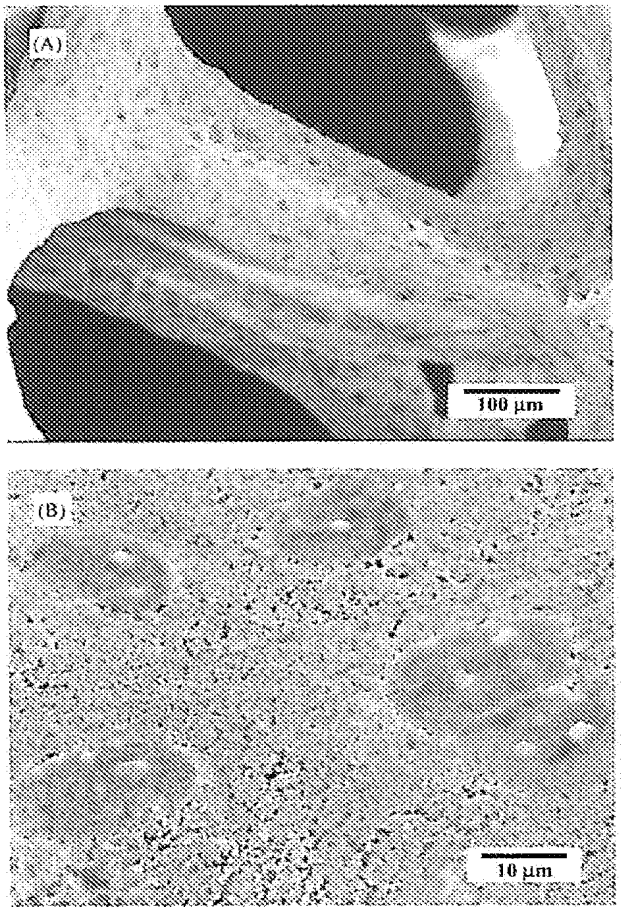

Fig. 7. SEM micrographs of the proliferated HOS cells on the HA/FA coated ZrO_2 porous body after culturing for 5 days: (A) at low and (B) at high magnification.

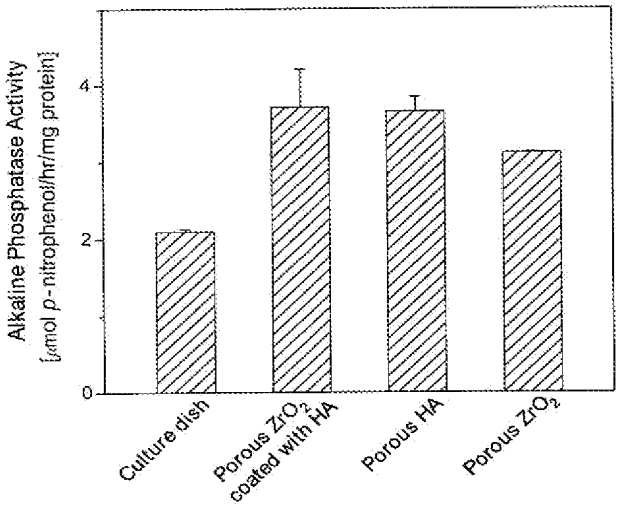

Fig. 8. Alkaline phosphatase activity of HOS cells on HA/FA coated ZrO_2 porous scaffold after culturing for 21 days; pure HA and ZrO_2 with same porosity were tested for the purpose of comparison. Plastic cell culture dish was used as a control.

4. Discussion

This study was undertaken to fabricate a bone scaffold with high mechanical strength and excellent biocompatibility. The porous HA has attracted much attention as bone substitutes because of its ability to lead osteoconduction. However, one of the main drawbacks for real applications is its poor mechanical property. To overcome this problem, coating of HA onto ZrO_2 porous body was derived.

Among many fabrication methods, the reticulated foam approach was adopted in this study, where the polyurethane template was replicated with ceramic slurries. This was found to be quite effective in obtaining highly porous structures. It is possible to change the porosity widely (92–74%) by just repeating the replication process. The porous structures obtained in this study, with a large pore size ($\sim$600 μm) and high porosities, are expected to be sufficient to permit tissue ingrowth and anchor the prosthesis to the surrounding bone as well as to supply blood and nutrients to the bone-like vascular canals. At a relatively high porosity, the initial polyurethane foam structure was exactly replicated with perfectly interconnected open pores. However, when the porosity approached to 70%, the pores were partly blocked as a result of thicker stems.

The obtained ZrO_2 scaffolds with various porosities exhibited an excellent compressive strength; 1.6–35 MPa when the porosities were between 92% and 74%. The values were superior to those of HA by a factor of 7. When considering the compressive strength of cancellous bone (2–12 MPa), the vales obtained in the ZrO_2 porous scaffolds can possibly be used as load-bearing parts [18,19].

The porous ZrO_2 body was coated with HA by the slurry method in order to render the biocompatibility. During the coating process, special precautions were needed to suppress the reaction between HA and ZrO_2. Previous studies showed that the direct contact of HA with ZrO_2 at elevated temperatures ($\sim$1150 °C) caused serious decomposition reactions [16,17]. Indeed, the HA coated on the ZrO_2 degraded into β- or α-TCP (see Fig. 4(A)) with a reaction byproduct of $CaZrO_3$, according to Eqs. (1) and (2).

$$Ca_{10}(PO_4)_6(OH)_2 + ZrO_2 = \beta\text{-}Ca_3(PO_4)_2 + CaZrO_3, \quad (1)$$

$$\beta\text{-}Ca_3(PO_4)_2 = \alpha\text{-}Ca_3(PO_4)_2. \quad (2)$$

The formation of TCP (β- or α-) at the interface of HA and ZrO_2 may cause serious problems because it is dissolved much faster than HA in a body fluid [20]. This result in a disintegration of the coating layer from the ZrO_2 substrate. The FA is known to have a superior chemical and thermal stability to HA [16,17]. Hence, in this study, FA was introduced as an intermediate layer between the HA and ZrO_2. As expected, there were no chemical reactions among the materials when the FA layer was introduced (see Fig. 4(B)).

The bonding between the HA and the FA in the HA/FA double layer appeared to be very high as observed by the SEM micrographs. This was attributed to the similarity in the chemical composition, crystallographic structure, and the sintering behaviors between the HA and the FA. However, the structure of the coating layer was rather porous with pore sizes of 1–2 μm. The micro-porous structure of the coating layer is known to induce an improved adhesion of the bone with implants through mechanical interlocking and consequently to promote osteointegration [21]. Moreover, the micro-porous structure has an advantage for the circulation of a physiological fluid through the coating and can therefore enhance the ingrowth of bone into the coating layer [22]. The intrinsic mechanical properties of the coating layer, such as the toughness and hardness, are expected to be somewhat down regulated due to the micro-porous structure. A suggestion might be raised to remove the micro-pores by introducing a sol–gel technique at a final coating step. Investigations into a sol–gel derived HA coating to fabricate a relatively dense layer is currently underway.

The mechanical property of the HA/FA double-layer on the ZrO_2 was evaluated by the adhesion strength test. In a coating system, bonding strength of the coating layer to the substrate is one of the most crucial parameters that determines the stability and longevity of the system. A poor bonding may result in a loss of fixation from the host tissues at the interface. The value

obtained in the HA/FA coated ZrO_2 was ~22 MPa, which was comparable to or slightly higher than reported values [23,24]. However, it is difficult to compare the strength values directly because of the differences in the coating thickness. The relatively high bonding strength was attributed to the relief of thermal mismatch between the HA/FA and ZrO_2 (due to porous structure of the coating layer) and also to the chemical inertness of FA with respect to ZrO_2 substrate. The coating layer always failed at the coating-substrate interface (Fig. 6), indicating a lower bonding capability between the FA and the ZrO_2 compared to the coating layer itself or the bonding between the HA and the FA.

To assess the cellular response, osteoblast-like cells (HOS) were cultured on the HA/FA coated ZrO_2. The cells adhered well to the material as confirmed by their spreading and growing morphologies (Fig. 7). Moreover, the migration and growth of the cells deep into the porous structure suggest the possibility of bone ingrowth into the porous structure. The cells differentiated further as evidenced by the alkaline phosphatase (ALP) activity of the HOS cells on the fabricated materials. The ALP activity has long been recognized as a marker for the functionality and activity of the osteoblast cells undergoing the differentiation step [25,26]. The higher ALP expression levels in the HA/FA coated ZrO_2 when compared to pure ZrO_2 showed that the cells were differentiating to a high degree. Along with the ALP test, other in vitro experiments are essential for deeper understanding of the activity and functionality of cells responding to the HA/FA coated ZrO_2 porous scaffolds.

At this point, a question might be raised on the chemical and mechanical stability of ZrO_2 porous scaffolds since the tetragonal ZrO_2 is known to undergo transformation to monoclinic phase at relatively low temperatures, leading to a severe degradation in mechanical properties. This process is generally called as low-temperature degradation or simply aging of ZrO_2. However, the aging of ZrO_2 occurs actively only in the temperature range of 200–400°C and in the presence of water vapor [27,28]. In practice, many researches on the degradation of yttria stabilized ZrO_2 reported no significant changes in chemical composition and/or reduction in mechanical properties under physiological environments (within bone marrow, subcutis, Ringer's solution, and HCl solution at 37°C) [29,30]. Moreover, in vivo tests on yttria stabilized ZrO_2 reported no adverse response of the ZrO_2 implant driven by a mechanical degradation. Based on those reports, the tetragonal ZrO_2 fabricated in this study seems to retain chemical stability and mechanical strength in a biological condition [31,32]. Nevertheless, in vivo animal tests remain as further study for complete understanding of the biocompatibility of the HA/FA coated ZrO_2 porous scaffolds.

5. Conclusions

Strong ZrO_2 porous bodies were successfully coated with biocompatible HA by inserting an inert FA intermediate layer. The ZrO_2 scaffolds with porosities ranging from 92% to 74% were obtained by repeating the replication cycles. These scaffolds exhibited superior compressive strengths compared to pure HA bodies with equivalent porosities by a factor of 7. The FA layer prevented the reaction between HA and ZrO_2 and suppressed the decomposition of HA. The obtained HA/FA coating layer with a thickness of ~30 μm was microporous and tightly bonded to the substrate (bonding strength ~22 MPa). In vitro cell tests showed good attachment and spreading of the HOS cells on the coating layer throughout the porous scaffolds. The proliferated cells on the HA/FA coated ZrO_2 scaffold represented a similar ALP expression level with respect to the pure HA and a higher level compared to the plastic culture dish and pure ZrO_2.

Acknowledgements

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EXHIBIT B

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September 5, 2006

SCHMEISER, OLSEN & WATTS LLP
Attn. Albert L. Schmeiser, Esq.
18 E. University Dr., Ste. 101
Mesa, AZ 85201
USA

Re: US. Patent Application No. 10/723,401
Entitled: Porous Bioceramics for Bone-Scaffold and Method for Manufacturing the Same
Your Ref No.: SECH-10159
Our Ref. No.: Patent-03-06US

Dear Mr. Schmeiser:

We have received with thanks your report as of August 18, 2006 for the office action from the United States Patent and Trademark Office.

The cited article "Porous ZrO2 bone scaffold coated with hydroxyapatite with fluorapatite intermediate layer" was published on August 19, 2003 which was before the U.S. filing date of this application, however the authors Messrs. Hae-Won Kim and Hyoun-Ee Kim are also the original applicants and inventors of this application. The other authors of the cited article, namely Seung-Yong Lee, Chang-Jun Bae, Yoon-Jung Noh, Hyun-Man Kim and Jea Seung Ko were just assistants for the inventions of this application, not inventors.

For your reference, a patent application with the same inventions was filed in Korea on December 1, 2003 within the Korean grace period (six months) from the publication date of the cited article and was granted and registered as a patent in Korea.

Since the inventions of this U.S. patent application and the cited article were actually made by the Messrs. Hae-Won Kim and Hyoun-Ee Kim and the other authors just assisted them for experiments, we consider that the inventions of this application shall be deemed to be invented before the publication date of the cited article

States Patent and Trademark Office.

The cited article "Porous ZrO2 bone scaffold coated with hydroxyapatite with fluorapatite intermediate layer" was published on August 19, 2003 which was before the U.S. filing date of this application, however the authors Messrs. Hae-Won Kim and Hyoun-Ee Kim are also the original applicants and inventors of this application. The other authors of the cited article, namely Seung-Yong Lee, Chang-Jun Bae, Yoon-Jung Noh, Hyun-Man Kim and Jea Seung Ko were just assistants for the inventions of this application, not inventors.

For your reference, a patent application with the same inventions was filed in Korea on December 1, 2003 within the Korean grace period (six months) from the publication date of the cited article and was granted and registered as a patent in Korea.

Since the inventions of this U.S. patent application and the cited article were actually made by the Messrs. Hae-Won Kim and Hyoun-Ee Kim and the other authors just assisted them for experiments, we consider that the inventions of this application shall be deemed to be invented before the publication date of the cited article

and that this application shall not be rejected based on the cited article. We think that the inventors and the other authors may make and submit an affidavit or declaration for the fact.

Therefore, please advise us of what we shall do for the grant of this application. If you need the declaration made by the inventors or the other authors, please provide us with its form or recommended text for the declaration.

If you need further information for this situation, please let us know.

Very truly yours,

Dr. Hyun Kim and Young-Dong Kim
Sechang Law Offices